Remarks

The Interview

Applicants and the undersigned greatly appreciate the examiner taking the time and effort to discuss the case. The interview provided the applicant with an opportunity to discuss the basis of the invention, the long standing problem with abuse where users extract drug from the formulation so that it can be injected or snorted, and the difficulties in making a formulation that is orally bioavailable but resists extraction. Dr. Fleming explained how much experimentation and research was required to develop a process which differs from that of the prior art by incorporating the drug into a lipophilic carrier material, not a formulation that just includes lipophilic material therein, which is then formulated. This requires a two step process: first incorporating the drug into the lipophilic material, then formulating, in contrast to the prior art method in which drug is just formulated using standard techniques.

Declaration of Dr. Alison Fleming

As also discussed with the examiner, comparative studies demonstrate that the differences in process of manufacture and materials produces a composition in which it is more difficult to extract the active agent than the formulation described in the prior art.

Amendments to the Claims

Claim 1 has been amended to refer to a therapeutically effective amount of a lipophilic drug or lipophilic derivative of a drug prone to abuse (as defined by original claim 1), and

(b) a formulation comprising carrier materials selected from the group consisting of fats, fatty substances, waxes, wax-like substances and mixtures thereof, (original dependent claims 18 and 19),

wherein the drug is dispersed within the carrier materials, which prevents the immediate release of a portion of incorporated drug when the physical integrity of the composition is compromised and the resulting material is exposed to water. (page 5, lines 3-13).

Claim 2 has been amended as an independent claim defining the carrier as slowly water soluble (page 14, lines 16-18) or water insoluble when the drug is a lipophilic derivative.

Water insoluble is defined in "The Pharmacopoeia of the United States Twenty-seventh Revision": as “An insoluble compound is one which requires greater than or equal to 10,000 parts of solvent (in this case, water) for 1 part of solute”.

Claims 4-7, 9-13, 15-17, 29, 35, 37, and 38 now depend directly or indirectly from claims 1 and/or 2.

Claims 14, 24, 25, 28, and 30-32 have been cancelled.

New claims 39 and 40 have been added.

Support for claim 39 is found at page 13, line 27 to page 14, line 12.

Support for claim 40 is found at page 19, lines 19-23.

Rejection under 35 U.S.C. 103

Claims 2, 4-7, 9-13, 16-26, and 33-36 were rejected as obvious under 35 U.S.C. 103 over U.S. Patent No. 6,310,072 to Smith in view of U.S. Patent No. 6,696,088 to Oshlack, et al. Claim 15 was rejected over Smith and Oshlack and further in view of

U.S. Patent No. 6,048,736 to Kosak or 5,756,483 to Merkus. These rejections are respectfully traversed.

U.S. Patent No. 6,310,072 to Smith

Smith discloses generally "dosage forms include tablets, dispersions, suspensions, injections, solutions, syrups, troches, capsules, suppositories, aerosols, transdermal patches and the like. These dosage forms may also include injecting or implanting controlled releasing devices designed specifically for this purpose or other forms of implants modified to act additionally in this fashion. Controlled release of the strong opioids may be affected by coating the same, for example, with hydrophobic polymers including acrylic resins, waxes, higher aliphatic alcohols, polylactic and polyglycolic acids and certain cellulose derivatives such as hydroxypropylmethyl cellulose. In addition, the controlled release may be affected by using other polymer matrices, liposomes and/or microspheres."

There is no disclosure of incorporating or dispersing the drug first into a lipophilic or water insoluble carrier.

U.S. Patent No. 6,696,088 to Oshlack

Oshlack is discussed in detail and compared to the claimed formulations in the accompanying Declaration of Dr. Fleming. Oshlack describes oxycodone formulations. These are mixed with another drug to make them less desirable to abusers who are unable to separate the oxycodone from the second drug when they extract the drugs from the carrier.

Oshlack discloses a formulation that prevents release of the second drug (antagonist) from the intact dosage form. This is achieved by coating the tablets with a

polymer such as an acrylic resin or hydroxycellulose. This does not prevent the drug from being extracted after the tablet is crushed, however, since the coating is disrupted by crushing. In fact, the coating is specifically designed to release the second drug upon crushing (*see* col. 8, line 64 to col. 9, line 6).

In contrast, since the drug is incorporated in water-insoluble particles and then formulated as defined by the claims in the present application, crushing does not disrupt the coating and the abuser still has great difficulty in extracting the oxycodone.

U.S. Patent No. 6,048,736 to Kosak

Kosak is similar to Oshlack in disclosing coatings that decrease extraction, but only until the tablet is crushed.

U.S. Patent No. 5,756,483 to Merkus

'483 teaches the nasal administration of a drug in combination with cyclodextrin (preferably methylated beta-cyclodextrin) or polysaccharide in order to improve the stability or bioavailability of the drug. The claims and specification disclose the formation of a complex between a drug and a poorly water soluble cyclodextrin (eg, ethylated beta-cyclodextrin) in order to achieve a lipophilic derivative of the drug (See paragraph 0040).

Based on the teachings of '483, it would not have been obvious to one of ordinary skill in the art to complex a drug with a cyclodextrin in order to form a lipophilic derivative of the drug, nor to incorporate it into a water insoluble carrier to reduce extractability.

None of the references disclose incorporation of a drug, especially a lipophilic drug or lipophilic drug derivative into a water insoluble or lipophilic material as claimed, nor the basic concept which is effective to reduce extractability even after crushing.

Favorable consideration of claims 1-13, 15-29 and 33-38 is respectfully solicited.

Respectfully submitted,

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